REMARKS

Applicants thank the Examiner for considering Applicants' response filed September 15, 2004, and for withdrawing the previous enablement, indefiniteness and double patenting rejections. Claims 1 and 26-35 were pending in this application. Claims 30 and 31 are withdrawn from consideration as they allegedly read on non-elected species. Claims 1, 26-29 and 32-35 have been rejected. Applicants amend claims 1 and 28 to recite the step of "determining said mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes" solely in an effort to facilitate prosecution. Support for the claim amendments can be found throughout the specification as-filed, for example, at least at page 34, lines 5-10. No new matter is added. Applicants cancel claim 35 without prejudice and reserve the right to pursue the subject matter of that claim in a continuation application.

Accordingly, claims 1, 26-29, 32 and 34 will remain pending upon the entry of this amendment.

Applicants respectfully request consideration and examination of this application and the timely allowance of the pending claims in view of the arguments below.

Written Description Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 26-29 and 32-35 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly lacking written description in the specification as filed. In particular, the Examiner alleges that the specification does not contain support for the limitations "determining said mammalian subject would benefit from inhibition of a

cytotoxic T cell response" and "determining the dose or dose range of an antibody directed to PSGL." (12/28/04 Office Action at page 2).

Applicants submit that the claims, as amended, no longer recite these limitations, thereby rendering this rejection moot. Accordingly, Applicants request that this rejection be withdrawn.

Indefiniteness Rejection under 35 U.S.C. § 112, second paragraph

Claims 1, 26-29 and 32-34 have been rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. In particular, the Examiner alleges that claims 1, 26-29 and 32-34 are indefinite in their recitation of "determining said mammalian subject would benefit from inhibition of a cytotoxic T cell response."

As discussed above, Applicants have amended instant claims to replace this limitation with "determining said mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes." Accordingly, Applicants respectfully request that this rejection be withdrawn.

Anticipation Rejection under 35 U.S.C. § 102(e) over *Cummings*

Claims 1, 26-29 and 32-34 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,667,036 to Cummings *et al.* ("*Cummings*").

The Examiner acknowledges that *Cummings* is silent about the inhibition of a cytotoxic T lymphocyte response. (12/28/04 Office Action at page 5). The Examiner, however, alleges that it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. *Id.* The Examiner further states that "merely discovering and claiming a new benefit of

an old process cannot render the process again patentable." The Examiner appears to contend that inhibition of a cytotoxic T cell response is an inherent property of a PSGL antagonist, by further stating that "mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *Id.*

A proper anticipation rejection requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. Further, to serve as an anticipation reference in an inherency rejection, the reference must make clear that the missing descriptive matter is necessarily present in the thing described in the reference. *Schering Corporation v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1376 (Fed. Cir. 2003).

The instant invention is based, at least in part, on the realization that antibodies directed to PSGL inhibit differentiation of activated proliferating T cells into cytotoxic lymphocytes. Applicants' specification shows that such antibodies are useful to treat diseases and conditions resulting from over-aggressive immune and inflammatory responses, such as, for example, allergic reactions and autoimmune diseases. Applicants' claims, as amended, recite the step of determining a mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes.

Cummings generally discusses that criteria for assessing a response to therapeutic modalities employing antibodies or carbohydrate is dictated by the specific condition. *See* col. 21, lines 25-28. Specifically, *Cummings* provides certain clinical indicia for determining effective dosage of PSGL antibodies to prevent extension of

myocardial infarction, acute respiratory distress syndrome, shock (low blood pressure), stroke, and organ transplant. *Id.*, lines 25-45. Applicants note that not only does *Cummings* fail to teach or suggest inhibition of a cytotoxic T cell response, as acknowledged by the Examiner, but *Cummings* also does not teach or suggest determining that a mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes, as recited by the amended claims.

Accordingly, Applicants submit that based on *Cummings*, one of ordinary skill in the art would have no motivation to use PSGL antibodies in a method which results in inhibition of cytotoxic response of a T lymphocyte (instant amended claim 1) or treats or ameliorates a disease or condition resulting from cytotoxic response of a T lymphocyte (instant amended claim 28), as *Cummings* does not even recognize that PSGL antibodies inhibit a cytotoxic T lymphocyte response. Furthermore, Applicants submit that even if administration of a PSGL antagonist to a subject inherently resulted in inhibition of a cytotoxic T lymphocyte response, as alleged by the Examiner, the additional step of determining the subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes is not present in the disclosure of *Cummings*, either explicitly or implicitly. Accordingly, *Cummings* fails to anticipate the claimed invention, either implicitly or explicitly.

In view of the foregoing, Applicants submit that the additional determining step renders the claims both novel and unobvious in view of *Cummings*, and request that this rejection be withdrawn.

Anticipation Rejection under 35 U.S.C. § 102(e) over *Larsen*

Claims 1, 2, 4, 26-29 and 32-34 are rejected under 35 U.S.C. §102(e) as being allegedly anticipated by U.S. Patent No. 6,277,975 to Larsen *et al.* ("*Larsen*").

The Examiner once again acknowledges that *Larsen* is silent about inhibition of a cytotoxic T lymphocyte response. (12/28/04 Office Action at page 5). The Examiner, however, contends that it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. As in case of *Cummings*, the Examiner again appears to contend that inhibition of cytotoxic T cell response is an inherent property of a PSGL antagonist, by stating that "mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *Id.*

Applicants respectfully traverse this rejection. Applicants have amended the claims to introduce the additional step of determining a subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes. *Larsen* fails to teach or suggest this limitation of the claimed invention, either implicitly or explicitly.

Larsen discusses use of PSGL antibodies, among other compounds which interfere with P-selectin binding, for modulating several functions relating to leukocyte adherence, inflammation, tumor metastases, and coagulation. *See* col. 18, lines 34-54. *Larsen* further discusses that neutralizing monoclonal antibodies to PSGL or to complex carbohydrates characteristic of PSGL may be useful therapeutics for both inflammatory diseases and some forms of cancer where abnormal expression of PSGL is involved.

See col. 20, lines 21-26. Applicants submit that not only does *Larsen* fail to teach or suggest inhibition of a cytotoxic T lymphocyte response, as acknowledged by the Examiner, but *Larsen* also does not teach or suggest determining a subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes. Additionally, even if inhibition of a cytotoxic T lymphocyte response was an inherent property of a PSGL antibody, as alleged by the Examiner, determining that a subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes is not anticipated or rendered obvious by *Larsen* and is a novel step in the methods of the claimed invention.

In view of the foregoing, Applicants submit that the pending claims are not anticipated or rendered obvious by *Larsen* and request withdrawal of this rejection.

Obviousness Rejection under 35 U.S.C. § 103(a) over *Cummings* and/or *Larsen* in view of *Snapp*, *Diacovo*, *Raychaudhuri* and *Rooney*

Claims 1, 26-29 and 35 are rejected as allegedly being obvious over *Cummings* and/or *Larsen* in view of Snapp et al. (Blood 91: 154-164 (1998)) ("*Snapp*"), Diacovo et al. (J. Exp. Med. 183:1193-1203 (1996)) ("*Diacovo*"), U.S. Patent No. 6,270,769 B1 to Raychaudhuri et al. ("*Raychaudhuri*") and U.S. Patent No. 5,962,318 to Rooney et al. ("*Rooney*").

Applicants respectfully traverse this rejection. A proper *prima facie* obviousness rejection requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there

must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. Also, see *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1443 (Fed. Cir. 1991) (the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure).

Applicants submit that not only has the Office failed to provide any motivation in the references themselves to combine them, but even if the references were combined, they fail to teach each and every limitation of the claimed invention, as discussed below.

(a) There is no motivation to use *Snapp* and *Diacovo* in the same rejection

Applicants note that *Snapp* and *Diacovo* appear to contradict each other, thereby providing no motivation to use them in the same rejection. For example, Applicants note that *Snapp* discusses that all T cells express PSGL and provides a monoclonal antibody to PSGL-1 which inhibited interactions between PSGL-1 and P-selectin. *See*, for example, page 154, column 2. *Diacovo*, to the contrary, discusses that not all T cells express PSGL-1. *Diacovo* further discusses that α/β T cells express PSGL and may express $CD8^+$, a hallmark of cytotoxic T lymphocyes; however, it is the T cells which do not necessarily express PSGL and do not express $CD8^+$ (γ/δ T cells) that have an enhanced ability to adhere to P-selectin, a characteristic of PSGL. *See*, Abstract. Based on this observation, one skilled in the art would not expect that a PSGL antibody would necessarily inhibit binding of $CD8^+$ α/β T cells to P-selectin when it is the $CD8^-$ γ/δ

T cells which do not necessarily express PSGL that show enhanced P-selectin binding. Thus, it would be improper to use both *Snapp* and *Diacovo* in the same rejection, as a skilled artisan would believe either *Snapp* or *Diacovo*, but could not consider the teachings of both the references to be accurate in light of their contradictions. Applicants address combinations of *Snapp* or *Diacovo* with the primary references separately for the sake of being fully responsive.

(b) Combination of *Cummings* and/or *Larsen*, *Snapp*, *Raychaudhuri* and *Rooney* fails to teach each and every limitation of the claimed invention

As discussed above, neither *Cummings* nor *Larsen* teach or suggest determining a mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes, either explicitly or implicitly. *Snapp* fails to cure the deficiencies of *Cummings* and *Larsen*. The Examiner has cited *Snapp* for the proposition that it teaches that all T cells, including $CD8^+$ cells, express high levels of PSGL-1, and that PSGL-1 is the principal or sole ligand for P-selectin on T cells. (12/28/04 Office Action at page 7).

Applicants note that *Snapp* discusses that all T cells express high levels of PSGL-1. *See*, Abstract. *Snapp* further discusses that a monoclonal antibody to PSGL-1 inhibited interactions between PSGL-1 and P-selectin. *See*, for example, page 154, column 2. Thus, while based on *Snapp* one of ordinary skill in the art may use an anti-PSGL antibody to inhibit an interaction between PSGL-1 on T cells and P-selectin, *Snapp* fails to provide any motivation or suggestion that such an antibody would be useful for inhibiting cytotoxic response of a T lymphocyte or for treating or ameliorating

a disease or condition resulting from cytotoxic response of a T lymphocyte, as recited by the instant claims. Additionally, *Snapp* also fails to teach or suggest determining a mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes.

Raychaudhuri and *Rooney* are simply cited as teaching methods of determining cytotoxic T lymphocyte function, and therefore are do not compensate for any deficiencies.

(c) Combination of *Cummings* and/or *Larsen, Diacovo, Raychaudhuri* and *Rooney* fails to teach each and every limitation of the claimed invention

As discussed above, neither *Cummings* nor *Larsen* teach or suggest determining a mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes, either explicitly or implicitly. *Diacovo* fails to cure the deficiencies of *Cummings* and *Larsen*. The Examiner has cited *Diacovo* for the proposition that it discusses that PSGL mediates P-selectin-dependent adhesion of myeloid cells, and that PSGL is present on α/β T cells and may serve a similar function on T cells. *Id.*

Applicants submit that *Diacovo* fails to teach or suggest that using an antibody to PSGL would be useful in inhibiting cytotoxic response of a T lymphocyte. T lymphocytes that elicit a cytotoxic response are those which express $CD8^+$, such as, α/β T cells. As discussed above, *Diacovo* discusses that it is the T cells which do not necessarily express PSGL and which do not express $CD8^+$ that have an enhanced ability to adhere to P-selectin, a characteristic of PSGL. *See,* Abstract. Thus, based on

Diacovo, one of ordinary skill in the art would expect an antibody to PSGL to have a greater effect on the interaction of γ/δ T cells with P-selectin than $CD8^+$ positive α/β T cells. Accordingly, such an antibody would not be expected to necessarily inhibit functions of $CD8^+$ positive cells, as alleged by the Examiner, as γ/δ T cells do not even express $CD8^+$. Additionally, *Diacovo* also does not teach the step of determining that a subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes.

Raychaudhuri and *Rooney* are simply cited as teaching methods of determining cytotoxic T lymphocyte function, and therefore are do not compensate for any deficiencies.

In view of the foregoing, Applicants submit that none of the cited references teach or suggest the concept of treating conditions associated with abnormal generation or function of cytotoxic T lymphocytes with an antibody to PSGL. Accordingly, Applicants request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejections and timely allowance of the pending claims. Should the Examiner feel that this application is not in condition for allowance, Applicants request that the Examiner contact the undersigned representative at 617-452-1606.

If there is any fee due in connection with the filing of this Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: March 25, 2005

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